

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: David J. Pinsky, et al.
U.S. Serial No.: 10/679,135 Examiner: J. Pak
Filed: October 3, 2003 Art Unit: 1616
For: A METHOD FOR TREATING ISCHEMIC DISORDER
USING CARBON MONOXIDE

1185 Avenue of the Americas
New York, New York 10036
December 20, 2006

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF IRVING L. KRON, M.D. UNDER 37 C.F.R. §1.132

1. I am a professor of surgery, Chairman of the Department of Surgery and Head of the Division of Thoracic and Cardiovascular Surgery at the University of Virginia in Charlottesville, Virginia. A copy of my *curriculum vitae* ("CV") is attached hereto as **Exhibit A**.
2. I have performed approximately 300 organ transplants, including approximately 150 organ transplants prior to September 27, 1996. I have also authored or co-authored more than 70 publications on the subject of organ transplantation, many of them prior to September 27, 1996. A complete list of my publications is attached to my CV (See **Exhibit A**).

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Exhibit 1

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3. I am familiar with the state of the art of organ transplantation as of September 27, 1996.
4. I have been provided with, and have reviewed, the specification of U.S. patent application Serial No. 10/679,135 filed in the name of David J. Pinsky, et al. entitled "Method for Treating Ischemic Disorder Using Carbon Monoxide" ("Application"), a copy of which is attached hereto as **Exhibit B**.
5. I have also been provided with, and have reviewed, the claims pending in the Application, i.e., 46, 49-62, 65, 89 and 90, the text of which is attached hereto as **Exhibit C**. I am advised and understand that only claim 46 is an independent claim and all other claims depend from and are subcases of claim 46.
6. I am advised, and understand, that the U.S. Patent Office Examiner reviewing the Application and the claims pending in the Application has rejected the claims on the basis that a person skilled in the art, reading the Application, would have understood the phrase "protectively treating a subject from an ischemic disorder as a result of organ transplantation" to refer to the organ donor only.
7. I am further advised, and understand, that the Examiner has taken this position because in Example 11 beginning on page 133, at line 34 of the Application, carbon monoxide was administered to rats whose lungs were later used in lung transplants, and there is no other experimental example

involving organ transplantation in the Application. In Example 11, the transplanted lungs were shown to confer improved arterial oxygenation to the recipient, increased pulmonary arterial blood flow and improved survival of the lung recipient, compared to recipients of lungs when the lung donor was not pretreated with carbon monoxide.

8. I certainly agree that Example 11 supports the conclusion that a donor of a transplanted organ can be protectively treated for an ischemic disorder by administering to the donor carbon monoxide prior to transplantation. However, I do not agree that a person skilled in the art would understand the term "subject" in the context of the Application to be limited to the donor of a transplanted organ.
9. First, I note that the term "subject" appears in the Application numerous times. Except in Example 11, each time organ transplantation is discussed, the term "subject" is used, never the term "donor." See, for example, page 19, line 36 and page 21, line 12.
10. Second, although the authors of the Application clearly understand the meaning of the term "donor" in an organ transplant context as shown by Example 11, they used the term "subject", not "donor", to broadly describe the types of persons involved in an organ transplant to whom carbon monoxide might be administered to protectively treat for ischemic injury.

11. Third, as of September 27, 1996, persons skilled in the art were well aware that ischemic injury or damage due to reperfusion frequently occurred in the recipient of a transplanted organ.
12. For example, McCord, J.M. "Oxygen-Derived Free Radicals in Post-Ischemic Tissue Injury", N. Engl. J. Med. 1985 Jan. 17; 312(3): 159-63 ("McCord") discusses, in relevant part, ischemic injury as a result of reperfusion in the recipient of a transplanted kidney. Specifically, at the bottom of column 2 on page 162, McCord states that "[a]nother example of iatrogenic ischemia is found in organ transplantation. A donated kidney may be removed from a cadaver, packed in ice, and maintained in a totally nonperfused state for many hours before being implanted and reperfused in the recipient [emphasis added]. The transplanted organ invariably suffers at least a temporary loss of function as a result of the ischemic insult, and acute tubular necrosis can lead to subsequent organ failure". The author goes on to state in the first paragraph on page 163 that research in methods of preventing ischemic insult is a fertile area not only for kidney transplants, but for heart, heart-lung, and liver transplants as well. A copy of McCord is attached hereto as **Exhibit D**.
13. Similarly, Unruh, H.W. "Lung Preservation and Lung Injury" Chest Surg. Clin. N. Am. 1995 Feb.; 5(1): 91-106 ("Unruh") supports the position that ischemic injury following reperfusion of a transplanted organ frequently occurs in the recipient of a transplanted organ. Specifically, on

page 103, Unruh states "[w]ith reperfusion, another phase of lung injury begins as the ischemic lung [in the recipient] is overloaded with oxygen and oxygen free radicals are generated." A copy of Unruh is attached hereto as **Exhibit E**.

14. Further, Novick, R.J., et al. "New Trends in Lung Preservation: A Collective Review", J. Heart Lung Transplant. 1992 Mar-Apr; 11 (2 Pt 1): 377-92 ("Novick") also discuss, in relevant part, ischemic injury caused by reperfusion in the recipient of a transplanted lung. Specifically, as Novick states in the last paragraph of column 2 on page 383, "[d]espite optimal techniques of harvest and storage, the lungs are exquisitely sensitive to reperfusion injury [in the recipient of the lung] after prolonged preservation." A copy of Novick is attached hereto as **Exhibit F**.
15. The preceding publications described in paragraphs 12-14 are merely representative of a much broader literature concerning the occurrence of ischemic injury or damage in recipients of organ transplants.
16. Fourth, as of September 27, 1996, persons skilled in the art regularly used the term a "subject" undergoing organ transplantation to refer to the recipient of the transplanted organ. Merely, by way of example, I have attached as **Exhibits G, H, I, J and K**, respectively, copies of the following abstracts:

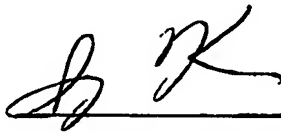
- G. Johnson, C.P., et al. "Factors influencing weight gain after renal transplantation", Transplantation. 1993 Oct.; 56(4): 822-7;
- H. Murphy, B.G., et al. "Effect of immunosuppressive drug regime on cardiovascular risk profile following kidney transplantation", Atherosclerosis. 1995 Aug.; 116(2): 241-5;
- I. Weston, M.W., et al. "Normalization of circulating atrial natriuretic peptides in cardiac transplant recipients", Am. Heart J. 1994 Jan.; 127(1): 129-42;
- J. Lambert, S.B., et al. "Bronchoalveolar lavage fluid endotoxin elevation in human single lung transplant recipients during rejection", Transpl. Immunol. 1995 Mar.; 3(1):81-5; and
- K. Keeffe, E.B. et al., "Controversies in patient selection for liver transplantation", West. J. Med. 1993 Nov.; 159(5):586-93.

In each of these abstracts, the authors use the term "subject" to refer to the "recipient" of the transplanted organ. Each of these abstracts have been marked to show where these terms occur.

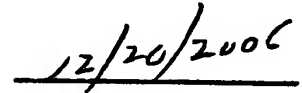
- 17. Based on the reasons referred to in preceding paragraphs 9-16, as well as my extensive experience in the field of organ transplantation, I am confident that persons skilled

in the art reading the Application would have understood that (a) the "subject" involved in organ transplantation includes both the donor and the recipient, both of whom were at risk for ischemic injury or damage due to reperfusion which necessarily occurs in both donor and recipient during organ transplantation surgery; and (b) treatment of the "subject" with carbon monoxide would have been desirable for treating both the donor and the recipient.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing thereon.



Irving L. Kron, M.D.



Date